[Frontiers in Bioscience E4, 195-204, January 1, 2012]

Dietary patterns and prostatic diseases

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1. ABSTRACT

Dietary patterns play a role on prostatic diseases in association with genetic, behavioral, occupational and environmental ones. Data from reviewed literature provide evidences of a possible relationship between dietary habits and the incidence of prostate disorders, even if it is not enough to justify a widespread adoption of new dietary habits. In this review the role of dietary patterns, including the use of supplements, in the prevention and treatment of the most frequent and known prostatic diseases, benign prostatic hyperplasia (BPH) and prostate cancer (PC) was analyzed. A limited number of well designed trials were identified in which diet and dietary supplement intervention appeared to slow disease progression. Although conclusive evidences are limited, the current data suggest that a diet low in total calories and fat, high in vegetables and fruits and that body weight control could be possibly effective in preventing prostatic diseases. On the other hand care must be taken to ensure that over-consumption of dietary supplements does not occur because it may be harmful.

2. INTRODUCTION

Descriptive epidemiology suggests that the incidence and prevalence of prostatic diseases vary significantly in different areas of the world (1-3). Possible reasons for such wide variations have been explored and nutritional factors were found to play a role together with genetic, behavioral, occupational and environmental ones. Overall dietary patterns, such as total caloric intake, macronutrients (carbohydrates, proteins and fat) and micronutrients (vitamins and minerals), and consumption of specific groups of foods are considered to be of importance in maintaining good health. In particular, fruits and vegetables are known to have a chemopreventive effect and according to the National Cancer Institute, about 400 compounds have been listed as potential chemopreventive agents and about 40 of these are currently under clinical evaluation (4). Different mechanisms for the observed chemopreventive effects have been described including antioxidant effects, anti-inflammatory activity, modulation of steroid metabolism, antibacterial and antiviral effects,

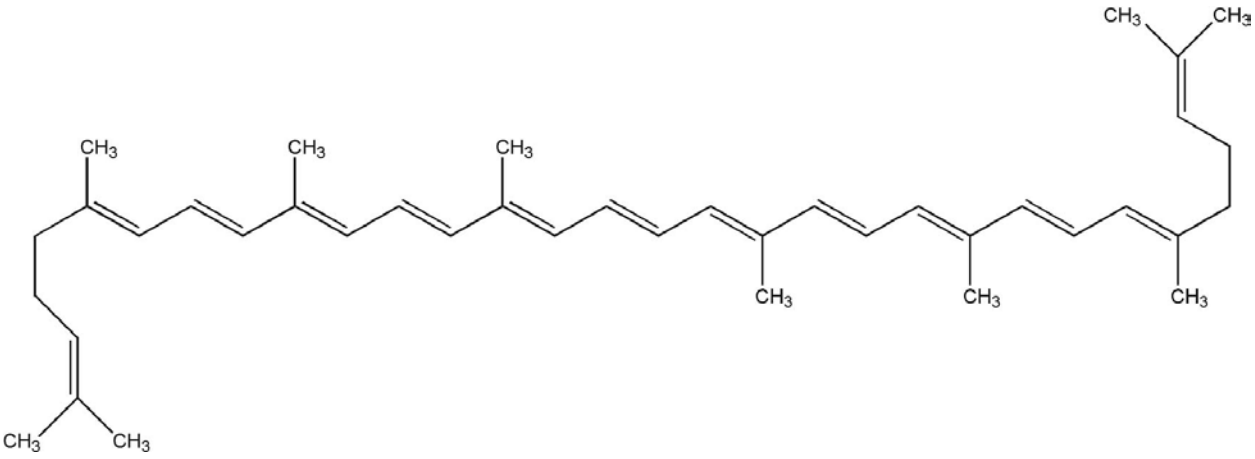

Figure 1. Lycopene structure.

modulation of detoxifying enzymes, stimulation of the immune response and antineoplastic effects. Data from epidemiologic studies provide evidence of a possible significant relationship between dietary patterns and the incidence of prostate disorders but not enough, per se, to justify a widespread adoption of new dietary habits. One of the reason is that the effects of dietary habits is difficult to investigate because they are rarely evaluated using validated questionnaires. Furthermore, the biochemistry of vegetables and fruits is quite complex and sometimes the therapeutic effect of a dietary factor supposed to be the active component often fails to replicate the therapeutic effect of the parent vegetable/fruit. There is a large volume of published studies describing the role of diet in the prevention and treatment of the two most frequent and known prostatic diseases, benign prostatic hyperplasia (BPH) and prostate cancer (PC). Although conclusive evidence is limited, the current data are indicative that a diet low in fat, high in vegetables and fruits and avoiding high energy intake is possibly effective in preventing and treatment these two conditions. This article systematically reviews the data of influence of dietary patterns on the prevention, treatment and management of prostatic diseases.

3. CAROTENOIDS

3.1. Lycopene

Carotenoids, mainly found in yellow/orange vegetables/fruits and cruciferous vegetables, are proposed to retard cancer-cell development and inhibit tumour promotion (5). Flavonoids have antioxidant properties (5), leading to the binding of free radicals and the reduction of oxidative damage of DNA and possibly cancer (6). In particular, several studies have evaluated the protective role exerted by lycopene against prostate disease. Lycopene is a carotenoid, mainly found in tomatoes and watermelon, which is proposed to limit oxidative damage to cellular macromolecules (Figure 1). Epidemiological evidence links lycopene consumption with decreased prostate cancer risk. Several signaling pathways have been identified as players in prostate cancer development. For example, chronic prostatitis due to infections is a suggested risk factor for prostate cancer. Endogenous production of reactive oxygen species during inflammation may lead to oxidative DNA damage, which can be mutagenic, if unrepaired. Androgen signaling, cytokine (IL-6, IL-4) and growth factor signaling (e.g., IGF, Wnt/beta-catenin) cross-talk via PI3K/Akt, MAPK, and Jak/STAT pathways have been identified as major controllers of prostate growth. Lycopene modulates several of the aforementioned pathways and in many experimental setups, lycopene reduced inflammatory signals, prevented oxidative DNA damage, modulated the expression or activity of IGF axis members, of Wnt/beta-catenin and androgen signalling, and enhanced gap junctional communication (7). A substantial part of the lycopene effects can be explained by its antioxidant action, but other mechanisms might also be involved. In vitro, lycopene impacts on insulin-like growth factor 1 (IGF-1) signaling, where high IGF-1 levels have been correlated with an increased susceptibility to PC (8). In epidemiological studies, regular intake of lycopene and high blood levels of the carotenoid have been repeatedly associated with a reduced risk of developing PC. Experimental studies have shown that lycopene inhibits progression of prostate tumour growth and PCa cell proliferation as recently reviewed by Clinton (9,10). In a case-control studies, lycopene consumption was inversely associated with the occurrence of PC (11,12) and tomato intake and serum lycopene levels were linked with a reduction incidence of advanced PC or the progression of PC in three recent case-control studies (13-15). Two large cohort studies have, however shown that tomato products and lycopene do not appear to prevent the incidence of PC (15,16). A meta-analysis of 11 case-control and ten cohort studies found an association between lycopene intake and a decreased risk of PC (17). Several evidences, based on both cohort and case-control studies, suggest that tomato/lycopene has a protective effect against PC (18). Lycopene was singly tested in two studies and in combination with several other agents, including soy isoflavones, in another one. Positive outcomes for lycopene supplementation either alone or in combination with other agents were reported in 2 of these studies (19-21). Ansari and Gupta (21) tested the effects of lycopene in advanced disease reporting a statistically significant difference in

PSA between the lycopene (4 mg) and orchiectomy treated group and control group of men with metastatic disease who underwent orchiectomy. Schroder (20) reported a significant increase of free PSADT (1,150 vs 445 days) in the protocol group compared to controls. This latter was a crossover study of 15 mg lycopene and multiple other compounds in men treated for 10 weeks with a 4-week washout period (24-week study). In the second treated group (intent to treat) there was a nonsignificant trend in PSADT increase and no difference in total or free PSA. In the remaining study no statistically significant benefits on PSA from lycopene supplementation were reported (19). The anti-neoplastic activity of lycopene it has been evaluated in a recent study by Zhang (22), who evaluated the impact of dietary lycopene on DNA synthesis, activity and expression of the androgen receptor gene in prostate LnCaP cells and found that lycopene inhibits DNA synthesis, androgen receptor gene element activity and expression in a dose-dependent pattern. Therefore lycopene may play an important role in prostate cancer cell proliferation. The exact molecular mechanism of antitumor activity of lycopene is unknown. Several evidences suggest that cancer cells have abnormal cholesterol biosynthetic pathways and prenylation of small GTPase proteins. A study conduct by da Palozza (23) showed that lycopene may exert its antitumor effects through changes in mevalonate pathway and in Ras activation. Incubation of the Ras-activated prostatic carcinoma LNCaP cells, with a 24-h lycopene treatment (2.5-10 muM) dose-dependently reduced intracellular total cholesterol by decreasing 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase expression and by inactivating Ras, as evidenced by its translocation from cell membranes to cytosol. Concomitantly, lycopene reduced the Ras-dependent activation of NF-kB. Such a reduction was parallel to an inhibition of ROS production and to a decrease in the phosphorylation of JNK, ERK1/2 and p38. These effects were also accompanied by an arrest of cell cycle progression and by apoptosis induction, as evidenced by a decrease in cyclin D1 and pAKT levels, and by an increase in p21, p27 and p53 levels and in Bax/Bcl-2 ratio (23). In summary, the evidence available to date suggests that a high versus low intake of foods containing lycopene could decrease the risk of PC. A possibly beneficial role of lycopene in patients diagnosed with benign prostate hyperplasia (BPH) has been suggested, although clinical data are lacking (24-27). A pilot study has investigated the effects of lycopene supplementation in elderly men diagnosed with BPH. A total of 40 patients with histologically proven BPH free to PCa were randomized to receive either lycopene at dose of 15 mg/d or placebo for 6 mo. The results showed that 6 mo of lycopene supplmentation decreased PSA levels, improved symptoms and inhibited progression of BPH (28). Interestingly, there was no selective interference of lycopene with PSA levels, which is important to allow early detection of PCa during long-term intake of supplements (28). Indications for potential inhibitory effects of lycopene on disease progression in BPH exist from a clinical pilto study in PCa patients showing induction of apoptosis by lycopene in cancer free BPH tissue (24). From in vitro studies, it is known that lycopene inhibits proliferation of benign prostate epithelial cells (25). The underlying mechanism may be inhibition of 5-alpha-reductase and interleukin-6 signaling, as demostrated in benign prostate tissue of rats (26). Moreover, because lycopene is an antioxidant, it may play a role in the oxidative stress-mediated cell proliferation and remodelling in benign prostate tissue (29).

3.2 Beta-carotene

Beta-carotene is a carotenoid that is converted to vitamin A in the gut. In a study has showed that high-dose beta-carotene intake leads to an increase in the risk of lung cancer and all-cause mortality in smokers (30). Interestingly, in three cohort studies no increase in risk of PC was noted with ≤ 25 mg β-carotene day (31,32). The Carotene and Retinol Efficacy Trial (CARET), a randomized, double-blind, placebo controlled trial testing a daily dose of 30 mg β-carotene + 25,000 IU retinyl palmitate showed, after an average of 11 years of follow-up that neither the CARET nor other supplements were associated with total prostate cancer risk but for aggressive prostate cancer; subjects in the CARET intervention arm who used additional supplements had a 52% increased risk of aggressive prostate cancer (Gleason ≥7 or stage III/IV) compared with all men in the placebo arm or those who used only the CARET vitamins (33). For no aggressive prostate cancer, men in the active CARET arm not using other supplements had a statistically significant 35% reduced risk of cancer compared with the referent, but there were no other significant associations of the CARET vitamins (with or without other supplements) with nonaggressive prostate cancer (33). These results are consistent with some, but not all, previously published reports. Two cohort studies have reported a finding of increased risk of fatal or aggressive prostate cancer among dietary supplement users compared with nonusers (34,35). One of these studies, the AARP cohort, reported the greatest risk among men using excessive multivitamins or more than one preparation per day. From reports of randomized, controlled trials, the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study reported a lower risk of prostate cancer in men randomized to the α-tocopherol arm of the trial, no effect for the α-tocopherol plus β-carotene arm, and a slight no significant increase in prostate cancer risk for the β-carotene only arm (36). There was no association detected in the Physicians Health Study, a randomized trial of aspirin and 50 mg beta-carotene on alternate days (37), but beta-carotene was associated with an increased risk of aggressive prostate cancer in a nested case-control study using data from the Prostate, Lung, Colorectal, and Ovarian Trial (5). In conclusion, results for beta-carotene and prostate cancer risk have been inconsistent. It was suggested that high beta-carotene intake may increase the risk of prostate cancer. Much remains to be learned about the effects of antioxidant catotenoids supplements on normal and neoplastic cells. Taken together, the results available suggests that dietary supplements, particularly multiple supplements or those used in large pharmacologic doses, should be used with caution especially if men have existing risk factor for prostate cancer.

4. GREEN TEA

Tea is considered the most popular beverage consumed in the world after water. There are three main

types of tea: green, black and oolong. Green tea accounts for 30% of all the product (38). Recent studies indicate that green tea (Camellia sinensis) may have a role in prostate cancer prevention. A prospective study has investigated the association between green tea consumption and risk of prostate cancer in Japanese men. In this study green tea consumption was associated with a decreased risk of advanced prostate cancer but no association was found between consumption and localized prostate cancer. In practice it seems that the effects of green tea differ according to cancer stage (39). The cancer-chemopreventive effects of green tea appear to be mediated by the polyphenolic constituents present therein. It was found that the major polyphenolic constituent (epigallocatechin-3-gallate) of green tea acts on various mechanisms of cancer pathogenesis: induces apoptosis, inhibits cell growth and arrests progression of the cell cycle. In particular epigallocatechin-3-gallate seems to inhibit tumour cell invasion and the expression of matrix metalloprotease, which is overexpressed in angiogenesis (40). Furthermore, other studies have shown that polyphenols also exert their effects through scavenging reactive oxygen species (ROS), since the excessive production of ROS has been implicated in the development of prostate cancer (41). A study has tested the effect of epigallocatechin-3-gallate alone and in combination with specific COX-2 inhibitors on the growth and apoptosis of human prostate cancer cells both in vitro and in vivo. This study demonstrated a synergistic action and an increased efficacy of selective COX-2 inhibitors in combination with green tea polyphenols for inhibition of growth of human prostate cancer cells both in vitro and in vivo. Authors concluded that the effect was attributed to increased activation of caspase-6 and caspase-9 leading to apoptosis and suggested that the combination of low doses of selective COX-2 with polyphenols from green tea may have a role in preventing prostate cancer (42). A trial conducted in Italy studied the effects of green tea polyphenols in males with high-grade prostate intraepithelial neoplasia (HG-PIN). In this double-blind, placebo-controlled study, 60 volunteers, with HG-PIN lesions, were enrolled to investigate whether the administration of green tea catechins could prevent progression of prostate cancer. This was the first study that has shown the effectiveness of green tea polyphenols for the treatment of pre-malignant lesions of prostate cancer. Concerning BPH, studies in the literature to evaluate the effect of geen tea on this disease are limited. In a recent study was observed that administration of green tea catechins reduced lower urinary tract symptoms, suggesting that these compounds could be used to treat symptoms of benign prostate hyperplasia (43). However, further studies are needed so that the polyphenols in green tea can be safely considered as chemopreventive agents for prostate cancer, furthermore, data on the effectiveness on BPH are limited.

5. PHYTOESTROGENS (ISOFLAVONES)

Phytoestrogens are naturally occurring phenolic plant compounds classified as flavones, isoflavones, coumestans and lignans. They are highly concentrated in soy products (beans, tofu) whereas plant lignans are found in legumes, whole grain, and various seeds and vegetables (44,45). Genistein, the predominant isoflavone in human nutrition, is derived mainly from soybeans but also from other legumes, including peas, lentils or beans. Numerous studies have been conducted on the effects of phytoestrogens in vivo and in vitro. Physiological concentrations of the soy-derived isoflavone genistein were shown to downregulate the androgen receptor of prostate cancer cells via the estrogen receptor beta, resulting in a modified response to hormonal stimuli (46). They also inhibit several steroid-metabolizing enzymes such as 5-alpha-reductase or aromatase (47,48). It has been postulated that these activities may be protective for prostate cancer by creating a more favorable hormonal milieu. Genistein is also able to inhibit growth and induce apoptosis in prostate cancer (49,50). In vivo studies have shown a significant reduction in the growth of prostate cancer in rats receiving diets rich in isoflavones (51). In spite of many available experimental data, there are few epidemiological studies that have assessed the direct relation between the individual dietary intake of soy products and other nutrients with phytoestrogens and the risk of prostate cancer. A study found that soy products were significantly protective on prostate cancer mortality. Prostate cancer mortality was inversely associated with estimated consumption of cereals, nuts, oilseeds and fish, particularly soy products were found to have an effect size per kilocalorie at least four times as large as that of any other dietary factor (52). However, the results of a recent review of studies on the direct relationship between dietary intake of soy products and risk of prostate cancer did not showed protective effects (53). In conclusion, nowadays it can not be demonstrated the efficacy of neither genistein nor other phytochemicals in the treatment of prostate cancer because of insufficient clinical evidence from studies. Nevertheless current available data prudentially allow recommending patients to use genistein with the aim to prevent the development of prostate cancer. Although it seems that isoflavones, but not lignans, have some influence on the benign prostatic growth, and that the prostatic concentration of genistein possibly has the closest association among them (54), additional studies are needed to clarify the roles and mechanisms of isoflavone action on benign prostatic hyperplasia, including pharmacokinetic studies.

6. SELENIUM

Selenium is an essential trace nutrient content in plants, animal products, and nutritional supplements. Natural food sources high in selenium include cereals (eg. corn, wheat, and rice), nuts (brazil nuts and walnuts), legumes (soybeans), animal products (beef, chicken, egg, cheese), seafood (tuna). It was assumed that selenium has a chemopreventive effect against a variety of malignancies including prostate cancer. Selenium would exert its anticarcinogenic properties by mean of apoptosis, inhibition of cellular proliferation, antiangiogenesis, and antioxidant pathways (55,56). As suggested by several studies, the antioxidant action could reduce DNA damage from free radicals and modulation of xenobiotic response

enzymes involved in carcinogen metabolism and clearance could reduce the impact of exogenous dietary carcinogens. A study also showed association between selenium level and genomic stability. In particular it was found a statistically significant relationship between low serum selenium and high overall levels of DNA damage (56). A multicenter cancer prevention trial, conducted between 1983 and 1991, attempted to determine whether a nutritional supplement of selenium will decrease the incidence of cancer, showed that supplemental selenium may reduce the incidence of and mortality from carcinomas of several sites (57). Another randomized, double-blind, placebo-controlled trial investigated the association between selenium and prostate cancer. This latter study provided support for the efficacy of selenium in reducing the incidence of prostate cancer basing on the observation that at the end of the trial the participants receiving a selenium supplement had a significantly lower incidence of prostate cancer than control group treated with placebo. In particular, it would appear that this effect was accentuated among men with the lowest baseline plasma selenium concentrations (58). However, the largest cancer chemoprevention trial ever conducted, the SELECT study, a phase 3 randomized, placebo-controlled trial failed to confirm that selenium, vitamin E, or both have a role in the prevention of prostate cancer in the generally healthy population (59). This trial was discontinued prematurely because there was no evidence of benefit from either study and there was no possibility of a benefit to the planned degree with additional follow-up.

7. VITAMIN E

"Vitamin E" is the collective name for a group of fat-soluble compounds that have antioxidant activities. There are eight chemical forms of vitamin E (alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol) that have varying levels of biological activity. Alpha-tocopherol is the only form that is recognized to meet human requirements. Vitamin E is found naturally in some foods, added to others, and available as a dietary supplement (60). It was found that vitamin E may intervene in the prevention of prostate cancer through its intracellular antioxidant properties (5). Several studies have investigated the association between vitamin E and prostate cancer. A case-control study showed that vitamin E intake was associated with a reduced risk of prostate cancer (61). A recent report from a clinical trial showed a reduction in the risk of developing prostate cancer by 33%, associated with supplementation with alpha-tocopherol. It has been suggested that this protective effect is related to the antioxidant effect of vitamin E (62). Previous studies suggested that the combination of carotenoids and tocopherols could be inversely associated with prostate cancer risk without to know how they affect prostate cancer progression and survival. A recent study has tested the effects of beta-carotene, alpha-tocopherol and retinol supplements on prostate cancer (63). Opinions were that higher baseline serum alpha-tocopherol was associated with improved cancer survival but neither serum beta-carotene nor retinol had a demonstrable effect. Longer prostate cancer survival was observed for those who recived alpha-tocopherol supplementation. It has been suggested that alpha tocopherol affects carcinogenesis by detoxifying oxiding radicals via its antioxidant properties, inducing cell cycle arrest in prostate cancer cells, decreasing cell growth by down-regulating the phosphoinositide 3-kinase pathway, enhancing cell-mediated immunity, targeting transcription factors, such as NF-κB, that contribute to malignant transformation and cell growth, and decreasing serum androgen concentrations. In contrast, many observational and intervention studies have not found association with beta-carotene, retinol and prostate cancer risk (63). Although these data would suggest that intake of vitamin E may reduce the risk of developing prostate cancer, especially in smokers and in those with low serum levels, extreme caution is needed before to introduce large quantities of this vitamin in the body, because as a study carried out in 2005, vitamin E consumption of over 400 IU may increase all-cause mortality (64).

8. FAT DIET

Dietary fat (particularly, saturated fat) and overweight/obesity are associated with prostate cancer and benign prostatic hyperplasia. This relashioship is based on in vivo and epidemiological data (65). Particularly, it was observed that high fat intake and obesity correlates with advanced PCa or aggresssive disease (66). A study demostrated an inverse association between the intake of monounsaturated fat and the risk of death from PCa (67). Another large cohort study also found that men who lose weight may reduce their risk of PCa (68). The data also suggest that a higher body mass index is associated with more aggressive or progressive diseases and a worse outcome (69). A low fat diet was investigated in a study conducted in 90 men with early stage prostate cancer on watchful waiting (70). A comprehensive lifestyle intervention program was evaluated including a low fat vegan diet providing 10% of total calories from fat and a significant 4% decrease in PSA was reported in the intervention group vs a 6% increase in controls at 1 years (70). A recent prospective, randomized dietary intervention trial in men with prostate cancer has evaluated the effect of a low fat diet on serum factors affecting prostate cancer cell growth (71). LNCaP cells were cultured in medium containing pre-intervention and post-intervention human serum to assess the in vitro effect of the diet on prostate cancer cell proliferation. It was observed that a low fat diet resulted in changes in serum fatty acid levels that were associated with decreased human LNCaP cancer cell growth. Correlation analysis revealed that decreased omega-6 and increased omega -3 fatty acid correlated with decreased serum stimulated LNCaP growth (71). Another study has evaluated the correlation between body mass index (BMI) and the food intake, especially fats and antioxidants, among subjects with PCa and those free of disease as a control group. The results showed that BMI in the subjects with PCa was higher than in controls but not statistically significant. However, there was a direct correlation between BMI and tumor aggressiveness (72). Total, saturated, monounsaturated and polyunsaturated fat intake was significantly higher in subjects with PCa, while

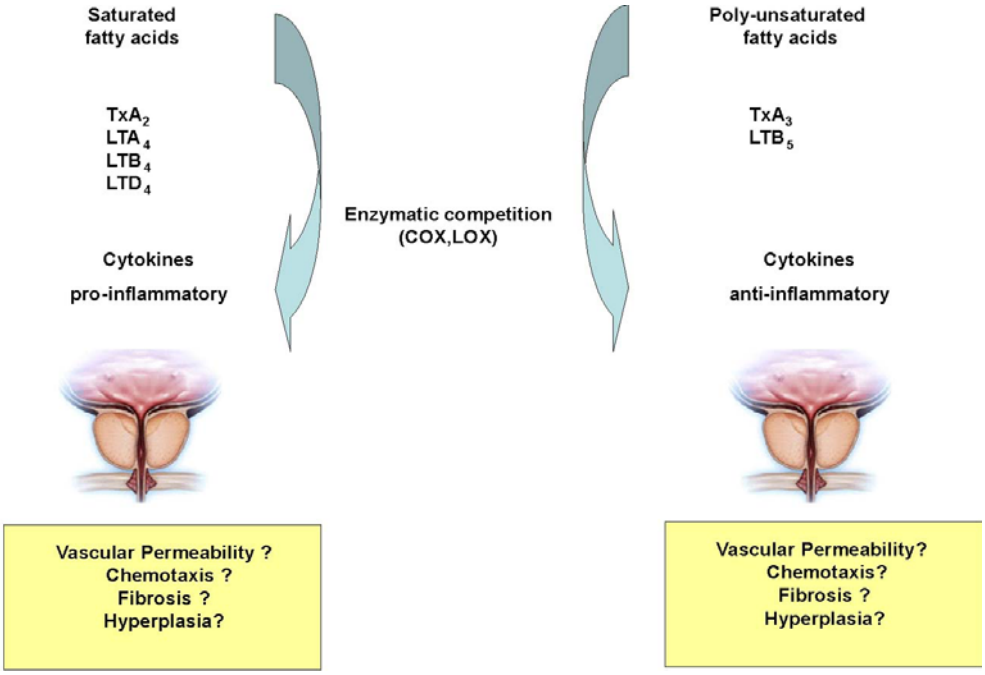

Figure 2. effects of saturated and unsaturated fatty acid on prostate

omega3 fatty acids intake was significantly lower than in controls (72). To delineate the molecular mechanisms underlying the enhanced progression of PCa under a high fat diet, a study investigated the differential gene expressions of a human PCa xenograft under high fat diet (HFD) and a low fat diet (LFD). LNCaP cells were subcutaneously injected in 20 nude mice, which were equally divided into two groups, the HFD group and LFD group. Oligonucleotide microarray analyses were performed using mice xenografts from HFD and LFD, and the results of candidate genes with a significant differential expression were validated by quantitative RT-PCR experiments. As for insulin-like growth factor I receptor (IGF-IR), protein expression levels were further examined by immunohistochemistry in xenograft tissues and in 78 radical prostatectomy specimens. The authors found that tumor volume and serum PSA levels were significantly higher in the HFD group than in the LFD group. 64 up-regulated genes and 14 down-regulated genes with more than twofold differences in the HFD xenograft were found. Immunostaining further revealed marked enhanced IGF-IR expression in the HFD xenograft. Is likely that high fat diet induced remarkable up- and down-regulation of mRNA of a substantial number of genes. Furthermore, the IGF-I system may be involved in the HFD-associated enhanced progression of PCa (73). Regarding BPH, little is known about its etiology, except for an involvement of androgens in its development and maintenance (74-76) and age-related changes in hormonal and other growth-regulatory factors that can cause cellular proliferation (77). However, the only well-established modifiable risk factor for BPH is obesity and, in particular, abdominal obesity (78-81). Dietary patterns that alter the hormonal milieu, such as a high-fat diet, or other regulator factors, such as insulin-like growth factors, could affect BPH risk. Also, prostate smooth muscle tone is controlled by the sympathetic nervous system, which is directly affected by many diet-related factors including energy intake, hyperglycemia and obesity (82,83). BPH may also be caused or exacerbated by chronic inflammation and subsequent oxidative damage (84), and thus dietary factors such as omega-3 fatty acids, polyunsaturated fats and antioxidants may also affect risk (Figure 2). A prospective cohort study examined dietary risk factors for incident benign prostatic hyperplasia (BPH) in 4,770 Prostate Cancer Prevention Trial (PCPT) placebo-arm partecipants who were free of BPH at baseline. The results showed that after 7-year of follow-up, BPH incidence rate increased with increasing age, body mass index (BMI) and waist/hip ratio (85). There were statistically significant increases in BPH risk associated with high pergentages of energy from total and polyunsaturated fats and read meat but there were no significant associations of any specific type of fat with risk (85). Interestingly, there were no associations of antioxidant nutrients, including supplemental vitamin E and selenium or total vitamin C with risk but it was showed that regular alcohol consumption was associated with reduced risk (85). Although, the risk was significantly lower in high consumers of vegetables (85). Others studies have investigated the influence of fat diet on BPH risk. The large study by Suzuki (86) reported modest increases in the 6 year period prevalence of BPH associated with high intakes of energy, animal protein, polyunsatureted fat and long-chain omega-3 fatty acids. Lagiou, in a very small case-control study, reported a nonsignificant increased risk associated with high intake of polyunsaturated fat (87). Although the current literature on BPH risk factor is quite limited, many of the dietary factors associable with BPH risk can also affect both steroid hormone concentrations and sympathetic nervous system. The dietary pattern

characterized by low fat, moderate alcohol, and high vegetables is associated with less obesity (88), lower serum estrogens and androgens, and higher sex hormone binding globulin (89,90) and probably also less sympathetic nervous stimulation (91). It is possible that these physiologic effects moderate both the hormonally regulated prostate growth and heightened smooth muscle tone that cause BPH. Planned future analyses, based on assays of serum steroid hormone, cytokine, and adipokine concentrations, may provide insight into whether these mechanisms underlie associations of diet with BPH risk.

9. SUMMARY AND PERSPECTIVE

Although the current data recommend a diet low in fat, high in vegetables and fruits, and avoiding high energy intake, there is no definitive evidence supporting a specific dietary therapy or dietary supplements for reducing the risk of prostate diseases. A limited number of randomized controlled trials are present in literature: many of these studies are affected from bias. More well designed randomized controlled trials could be useful to expand knowledge and replicate findings.

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Key Words: Prostate Cancer, Benign Prostatic Hyperplasia, Dietary Supplements

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